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Rubella in the developing world

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INTRODUCTION

Before Gregg's historic observation [1] rubella was not considered to have clinical or epidemiological importance in any country. In the western world epidemics occurred at varying intervals but with little morbidity and apparently only minor complications. Despite confirmation of Gregg's findings from many quarters, it was not until the worldwide outbreaks in the 1960s that the aftermath of rubella infection in pregnancy was fully realized. As a result of the 1964 outbreak in New York City, more than 1000 children were born with congenital rubella syndrome (CRS) and over 300 pregnancies either aborted spontaneously or were terminated for rubella infection [2]. The number of children affected represented 1% of births in the city; if extrapolated to the whole country this gave an estimated total of 30000 cases of CRS. No such disasters have so far been reported from the developing world.

RECOGNITION OF RUBELLA OUTBREAKS

In developed countries rubella commonly escapes notification since many cases are not seen by a doctor or even recognized by the patient. Nevertheless in the pre-vaccine era in the USA, clinical notifications identified rubella epidemics despite under-notification estimated to be as high as 30% [3]. In the UK clinical epidemics are confirmed by an increase in laboratory reports of infection, although these represent only a fraction of the total cases. On the other hand, a serological study in the UK in 1973 [4] confirmed rubella infection in only about half the clinically diagnosed cases. Thus serological confirmation is essential to establish both past and present rubella infection.

In developing countries rubella outbreaks can occur with no clinical recognition, even in a community in which health is being monitored. In a study in The Gambia, children from birth to 10 years were screened annually for rubella antibody from 1966–76 [5]. In 1966 only 14% of the children born in 1965 had rubella antibody, compared with 78% of the children born in 1964; a rubella epidemic had therefore occurred before the 1965 cohort was born. Children born between 1966 and 1972 remained serologically negative, but by 1974 a high proportion aged 1 year and over had acquired antibody, showing that a second rubella outbreak had occurred after a 10-year interval. Despite this serological evidence there were no clinical records of rubella during the period, and no instance of CRS in the Medical Research Council monitoring unit. Thus in developing countries, as in the west, the prevalence of rubella cannot be assessed without serological evidence.

RUBELLA SUSCEPTIBILITY

The incidence of rubella infection in pregnancy–and thus the risk of CRS–depends on the number of pregnant women in a population who are susceptible to rubella, together with evidence of rubella transmission in children. If rubella is circulating among children it is inevitable that among those infected will be rubella-susceptible women in the first trimester of pregnancy, when the risk of fetal damage is over 90% [6]. Serological studies have been undertaken in many developing countries to assess proportions of the population susceptible to rubella by age, and thus to define the degree of risk to women of child-bearing age. Results vary widely between countries, between different parts of the same country and, as reported above, over time in the same region.

Rubella susceptibility in women of child-bearing age

In a study reported in 1986 [7] Black and colleagues compared rubella antibody prevalence in pregnant women in 15 populations in Brazil, Chile, Ecuador, India, Nigeria, Jordan, South Africa, Taiwan and the United States. The lowest proportions of rubella-positive women aged 15–30 were found in four regions of Brazil (82%) and in the island of Tapei, Taiwan (87%). The highest immunity levels, 92–100%, were found in Chile, Lagos, Vellore, Nigeria, Jordan and South Africa. In Brazil the proportion of seropositive women increased with age, confirming a high risk of infection during the child-bearing years.

A report on rubella antibody prevalence in tropical Africa [8] showed wide variations in seropositivity in women of child-bearing age in different countries. In The Gambia, Ethiopia, Upper Volta and Uganda, 93% or more had acquired antibody by the age of 14; this is the probable explanation of the absence of CRS cases in The Gambia despite two serologically confirmed epidemics in the study mentioned above [5]. In Nigeria, Ghana, and Togo, however, 25–50% of women of child-bearing age were without antibody. The author concluded that rubella infection was widespread and endemic on the African continent, that outbreaks were occurring without recognition and that there were probably many more cases of CRS than those reported.

A study in three northern cities in India (Delhi, Chandigarh and Lucknow) and one eastern city (Calcutta) found that rubella antibody was present in 80% of women in the north, compared with only 57% of women in the east [9].

Serological evidence of rubella infection in pregnancy

A study in Brazil between 1974 and 1982 found that 91 of 7000 seronegative pregnant women acquired antibody during pregnancy showing that infection had occurred [10], but there was no follow up of the outcome. In the first year of the Indian study [9] none of the 28 seronegative women in Delhi seroconverted during their pregnancy. Two years later 6 of 19 seronegative women converted, with no apparent history of infection; all 6 babies were apparently normal at birth but were not followed up. In Lucknow, 62 of 300 pregnant women were seronegative; 4 seroconverted during their pregnancy after clinically inapparent rubella, Two who converted between 31 and 34 weeks delivered healthy babies; one who converted at 8–10 weeks aborted at 10 weeks, while the fourth who seroconverted

at 16–18 weeks delivered a baby with full CRS. The authors concluded that although rubella epidemics had never been reported in India, and contrary to the general medical belief, rubella infection was widespread in the country although the incidence of CRS was unknown.

Seropositivity according to age

Serological studies in children in the last 10 years in Jordan [11], Nigeria [12], Yemen [13], Saudi Arabia [14], Libya [15] and Taiwan [16] have all shown an increase in seropositivity with age. These and other studies already mentioned demonstrate that in many developing countries rubella infects children at different ages and that varying proportions of women have not acquired antibody when they reach child-bearing age.

Populations at particular risk

Studies in island and migrant populations show an increased risk of rubella infection in child-bearing age-groups. This is due to the lower seropositivity resulting from less chance of exposure to rubella in childhood. In addition to Taiwan [7], low immunity in the child-bearing years was reported from Okinawa and two of the West Indies [17–19]; subsequently severe rubella epidemics occurred in all these islands.

A study in Panama in 1989 [20] stressed the risk to women who migrated from rural areas where the chance of infection was low to cities where chances of contact with rubella were much higher; 71% of women in one rural community were susceptible to rubella compared with only 27% in a town populated by many recently arrived from other provinces. In Zimbabwe [21] an outbreak of rubella occurred in 1978 when large numbers of women and children moved from the country to the city. Following this, 18 cases of serologically confirmed CRS were diagnosed in one hospital, compared with the usual one or two annual cases.

MONITORING OF CRS CASES

It took a continent-wide rubella outbreak resulting in clustering of CRS cases in time before these were recognized for the first time by Gregg. Routine surveillance or passive notification of cases is unlikely to result in comprehensive reporting even in countries with sophisticated monitoring systems; in the US it was estimated that only 20% of cases were reported to the appropriate agency [22]. In developing countries, children with severe multiple defects probably die unrecognized during pregnancy or soon after birth; figures for rubella-related abortions or neonatal deaths are unlikely to be routinely available or reliable. However as Gregg showed, cataracts can be recognized in neonates in whom other rubella-associated defects may be present.

Recognition of neonatal cataract

A report in 1988 on childhood blindness [23] concluded that in countries with developing medical services, maternal rubella remained an important preventable cause of childhood cataract. The author stressed the need to train medical workers to recognize the condition, and the establishment of treatment centres. He concluded that of the world's estimated million children suffering from blindness,

up to three-quarters could be prevented by immunization against measles and rubella, combined with adequate intake of vitamin A and appropriate treatment of corneal ulceration.

Recognition of deafness

Passive notification may identify the more florid cases of CRS, but children with only degrees of sensorineural deafness may be missed and the true incidence of CRS remain unknown. Such cases are unlikely to be identified without a specific search. This was shown in Japan [24] where the apparently low incidence of CRS following rubella outbreaks – based on a routine reporting system – gave rise to the hypothesis that the rubella virus strain prevalent in Japan was less virulent than that which had caused the 1960s epidemics in Europe and America. However, a nationwide search for deaf children with a history of maternal rubella identified 365 cases in special schools, compared with 88 previously reported, The actual total was thought to be higher since many deaf children had been integrated into ordinary schools which were outside the study.

Clustered cases of rubella-related deafness in populations of children have been identified by comparing the prevalence of rubella antibody in children with and without sensorineural deafness. A study reported in 1979 of 568 children under 4 years attending a hearing and speech centre in London showed that 24% of 349 deaf children were seropositive for rubella compared with only 9% of 219 children who were not deaf [25]. In Australia a reduction in the number of schoolchildren requiring deaf aids has been used as an indication of falling maternal rubella infection [26–28].

IS RUBELLA A PROBLEM IN THE DEVELOPING WORLD?

The available evidence confirms that although conditions for rubella infection in pregnancy exist in many developing countries, CRS is seldom reported. Other viral infections, particularly HIV, currently dominate the need for medical services and finance. It may therefore be irrelevant to search for problems which apparently do not exist. However, if the introduction of rubella vaccine is contemplated, the local epidemiology and impact of rubella must be known before this is done. Seroepidemiological studies to establish antibody prevalence by age must be set up, together with a systematic search for cases of CRS; both must continue after the introduction of vaccine to monitor its effect.

Seroepidemiological studies

The age-range must cover children and women of child-bearing age and be locally based because of the wide variation. While a single survey provides basic information, a sequential study as in The Gambia [5] will show the epidemic pattern and thus give warning of possible clusters of CRS cases. Continuous serological data from pregnant women and confirmation of rubella infection in pregnancy are also required.

Systematic search for cases of CRS, with serological confirmation

(1) Examination for CRS of all infants born in hospitals over a period. This would be particularly valuable if serological surveillance showed evidence of a rubella outbreak.

(2) Search of hospital and clinic records in ear, eye and cardiac departments for children with rubella defects.

(3) Examination of school children for cataract and sensorineural deafness.

(4) Search among families in villages for babies and children with rubella defects and for causes of neonatal death, as proposed in the WHO neonatal tetanus study [29].

CHOICE OF POLICY

For developing countries with an existing measles vaccination programme in young children, the simplest and cheapest course would seem a combined measles/rubella vaccine. However, unless there are reliable records of a vaccine uptake exceeding 70%, rubella vaccination confined to this age-group may actually increase the age of infection and therefore the incidence of CRS. To avoid this, vaccination of pre-pubertal girls, as well as women before or after pregnancy, must precede or accompany vaccination of infants; vaccine uptake in the target age-groups must be recorded. This combined policy has now been adopted in both the USA and UK [30, 31].

COST EFFECTIVENESS OF VACCINE

The cost of rubella vaccination and monitoring programmes must be balanced against the cost of finding and treating cases of CRS. In the west, children with multiple defects are not only a family tragedy but a vast economical burden. In the US the direct annual national cost of care for individuals with multiple rubella defects was estimated in 1985 to be $90 million dollars, continuing for many years [32]. In Panama the cost for the first year of the 54 CRS cases born in 1986 was estimated to be equivalent to a quarter of the potential cost of vaccinating the whole of the Panamanian population from 1 to 34 years [20].

CONCLUSION

Rubella vaccine has now been in use in many developed countries for 20 years, but CRS has not been eliminated in any country with the possible exception of Sweden. Here the excellent monitoring programme has recorded no case of CRS since 1982, and no rubella infection in pregnancy between 1987–90. (M. Forsgren, personal communication). In developing countries the extent of the problem remains unknown. However the indiscriminate introduction of rubella vaccine without epidemiological data and an adequate monitoring programme should be avoided because of the very real danger of increasing the incidence of CRS.

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